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International Journal of Infectious Diseases 128 (2023) 223–229

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Lopinavir/ritonavir for treatment of non-hospitalized patients with COVID-19: a randomized clinical trial

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ARTICLE INFO

Article history:
Received 7 November 2022
Revised 19 December 2022
Accepted 21 December 2022

Keywords:
COVID-19
Antiviral
Outpatient
Lopinavir
Ritonavir
Clinical trial

ABSTRACT

Objectives: Effective and widely available therapies are still needed for outpatients with COVID-19. We aimed to evaluate the efficacy and safety of lopinavir/ritonavir (LPV/r) for early treatment of non-hospitalized individuals diagnosed with COVID-19.

Methods: This randomized, placebo (Plb)-controlled, double-blind, multi-site decentralized clinical trial enrolled non-hospitalized adults with confirmed SARS-CoV-2 infection and six or fewer days of acute respiratory infection symptoms who were randomized to either twice-daily oral LPV/r (400 mg/100 mg) or Plb for 14 days. Daily surveys on study days 1 through 16 and again on study day 28 evaluated symptoms, daily activities, and hospitalization status. The primary outcome was longitudinal change in an ordinal scale based on a combination of symptoms, activity, and hospitalization status through day 15 and was analyzed by use of a Bayesian longitudinal proportional odds logistic regression model for estimating the probability of a superior recovery for LPV/r over Plb (odds ratio >1).

Results: Between June 2020 and December 2021, 448 participants were randomized to receive either LPV/r (n = 216) or Plb (n = 221). The mean symptom duration before randomization was 4.3 days (SD 1.3). There were no differences between treatment groups through the first 15 days for the ordinal primary outcome (odds ratio 0.96; 95% credible interval: 0.66 to 1.41). There were 3.2% (n = 7) of LPV/r and 2.7% (n = 6) of Plb participants hospitalized by day 28. Serious adverse events did not differ between groups.

Conclusion: LPV/r did not significantly improve symptom resolution or reduce hospitalization in non-hospitalized participants with COVID-19.

Trial registration: ClinicalTrials.gov Identifier: NCT04372628

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https://doi.org/10.1016/j.ijid.2022.12.028

Introduction

COVID-19 remains a significant public health problem. There has been success in developing outpatient therapeutics such as neutralizing monoclonal antibodies, oral antivirals, and intermittent intravenous remdesivir infusions [1–7]. However, these treatments are costly, susceptible to resistance from new SARS-CoV-2 variants, and may not improve symptom resolution [8–11]. With increasing vaccination and less severe variants, hospitalization rates have declined [12–14], and the focus of initial treatment is now shifting toward acute symptom and functional recovery [15,16].

Lopinavir/ritonavir (LPV/r; Kaletra) is an HIV antiretroviral drug proposed for the treatment of COVID-19 based on promising *in vitro* data [17–21]. Its putative mechanism of action is through 3-CL protease inhibition [22–24], which is the same target as nirmatrelvir/ritonavir (Paxlovid), considered the first-line treatment for eligible symptomatic outpatients with COVID-19 [25]. Whereas nirmatrelvir/ritonavir is expensive and not globally available, LPV/r is relatively inexpensive, generic, widely available, and has a known safety profile. Previous trials for LPV/r in both inpatient [26–28] and outpatient [29] settings did not identify a meaningful benefit in treating COVID-19. However, treatment in previous trials was late in the course of the disease and potentially outside the therapeutic window. For example, in the outpatient TOGETHER trial, 84% of participants had experienced more than 5 days of symptoms before receiving treatment [29].

The Trial of Early Antiviral Therapies during Non-hospitalized Outpatient Window (TREAT NOW) was an adaptive platform trial to evaluate potential antiviral therapies for the treatment of COVID-19 among non-hospitalized individuals using a decentralized approach with a combination of local and remote recruitment, a single drug distribution center, and remote follow-up. We hypothesized that early administration of LPV/r would reduce disease progression and improve clinical outcomes among outpatient adults. Here we report the results of the TREAT NOW trial comparing LPV/r vs placebo (Plb).

Methods

Study design

The TREAT NOW platform protocol was a decentralized adaptive, blinded, multi-center, Plb-controlled randomized clinical trial to assess the efficacy and safety of different antiviral therapies in the outpatient treatment of COVID-19. The study initially included three arms: LPV/r, hydroxychloroquine, and Plb. As reported in the published protocol and statistical plan [30], the hydroxychloroquine arm was dropped early due to external evidence of a lack of efficacy. The protocol was approved by a single institutional review board at Vanderbilt University with reliance on local enrolling sites. Electronic, no-touch informed consent was obtained from each enrolled participant; consent from legally authorized representatives was not permitted.

Study participants

Participants had to be 18 years of age or older with a laboratory-confirmed SARS-CoV-2 infection by reverse transcriptase-polymerase chain reaction or another molecular test or by antigen test with emergency use authorization or full approval collected within the past 6 days. These results were confirmed with potential participants during the screening visit (typically remotely). Additionally, participants must have experienced at least one acute respiratory infection symptom within 6 days before randomization. Participants were excluded if hospitalized at time of enrollment. A full list of eligibility criteria, including medications, checked for drug-drug interactions, and enrollment procedures, are described in the Supplement and are summarized in the published protocol [30].

Randomization and blinding

We used a central electronic randomization system to allocate participants equally among enrolling study arms with stratification by enrolling site and age ($\geq$65 years or $<$65 years), given that risk for morbidity and mortality, and potential treatment response, is influenced by age. Study participants, treating clinicians, study personnel, and outcome assessors were blinded to allocation. Only the central study pharmacy and one member of the biostatistical team who prepared closed data and safety monitoring board (DSMB) reports were unblinded.

Interventions and treatments

Participants assigned to the LPV/r arm received 400 mg/100 mg twice daily for 28 doses (14 days total). Participants assigned to the Plb group received a generic oral Plb matching the LPV/r regimen.

The study drug was prepared by a central pharmacy (Belmar Pharmacy, Golden, Colorado) to provide the randomized treatment labeled by study day. Packaging of both LPV/r and Plb was designed to blind participants to their treatment assignment; the study drug was shipped to participants using overnight delivery.

Study procedures

To minimize contact with study personnel and enhance reach of recruitment, TREAT NOW employed a remote approach to assessing eligibility, obtaining informed consent, and collecting daily information via surveys on participant symptoms, adverse events (AEs), and location/status. We initially recruited participants from local health systems at five enrolling sites and then expanded to national recruitment using social media advertising. Once consented to and randomized, participants were sent surveys to collect medication adherence, symptoms, activities, and healthcare utilization daily for the first 16 days, then a final survey 28 days after randomization. “Baseline” refers to the day of randomization, and “Study Day 1” refers to the day with confirmed receipt of the study drug. Surveys could be completed via mobile device, computer, or over the phone with study personnel. Non-response for two consecutive days or events indicating potential AEs or hospitalization triggered telephone follow-up from research staff.

Outcomes

The primary outcome was a modification of the World Health Organization clinical status scale [31] measured longitudinally through day 15 of the study. To reflect the mild to moderate severity of disease in the outpatient setting, the modifications were to include three non-hospitalized states (no symptoms, symptoms without activity limitations, symptoms with activity limitations), three hospitalized states based on supplemental oxygen use (no supplemental oxygen, on supplemental oxygen, on mechanical ventilation or extracorporeal membrane oxygenation), or death. Using the serially collected clinical status through day 15 of the study allows the changes over treatment to be included in the analysis of the primary outcome, rather than using a non-longitudinal summary which would obscure the trends over time. Additional details can be found in Kaizer et al. [30] and the Supplement.

Secondary outcomes include the modified ordinal outcome on days 8 and 29, the proportion of patients hospitalized, time to hospitalization, time to symptom resolution, all-cause mortality, oxygen-free days, fever-free days, ventilator-free days, vasopressor-free days, intensive care unit-free days, and hospital-free days. Unless otherwise noted, all secondary outcomes are through the final participant survey on day 29.

Safety outcomes included all potential associated AEs, as well as seizure, atrial or ventricular arrhythmia, cardiac arrest, receipt of renal replacement therapy, severe dermatologic reaction, and others that are described in the protocol (Supplement).

Statistical analysis

The sample size was based on a frequentist proportional odds model with 90% power to detect an odds ratio (OR) of 1.75, assuming a 5% type I error rate. To account for an expected 10% loss to follow-up rate, 300 participants were needed per arm. The power calculation was based on limited preliminary data, given the emerging pandemic in May 2020. We prespecified interim monitoring rules for approximately 25%, 50%, and 75% of total enrollment based on the posterior probability of efficacy >95% or the posterior probability of inefficacy being >90%, with futility monitoring based on the predictive probability of success is less than 10%. Additional details on the power analysis and interim monitoring approach were previously described [30].

The primary analysis used a Bayesian longitudinal proportional odds model with a random intercept for each participant. We evaluated the proportional odds assumption with graphical methods, with the plan to use a partial- or non-proportional odds model if assumptions were clearly violated. To account for non-linear effects of treatment over the course of treatment, all analyses included a restricted cubic spline with four knots and a treatment-by-time interaction. The prior for the intercept assumed a Dirichlet distribution, and the priors for all other coefficients assumed a normal distribution with a mean of 0 and SD of 10. For adjusted models, prespecified covariates were race/ethnicity, age, sex, symptom duration (in days), presence of any predefined comorbidities, receipt of monoclonal antibody treatment, vaccination status, and time period of the trial broken into 3-month quarters. With respect to missing data, the chosen Bayesian methods do not require imputation for missing time points, assuming a missing at-random assumption conditional on the baseline covariates and previous time points. ORs greater than one indicate a benefit for LPV/r.

Subgroup analyses of the primary outcome included age, sex, race/ethnicity, body mass index, baseline renal function, hypertension, diabetes mellitus, cardiovascular disease, and duration of respiratory symptoms before randomization. For each subgroup, the unadjusted model was fit, with the addition of the subgroup variable without and with interaction with treatment. To facilitate a more parsimonious approach to determining if an interaction effect may be present, Bayesian stacking was then used to compare the two models. If the model with an interaction had a posterior weight of 80% or greater from the stacking procedure, models would then be fit within the respective subgroups. Exploratory analyses evaluated the severity of each symptom included in the primary outcome using the same unadjusted model. Secondary and safety outcomes are presented descriptively.

The main analysis used a modified intention-to-treat principle, where every participant with receipt of the study drug delivered from the central pharmacy is included. We used R software, version 4.1.0 (Vienna, Austria), for the analyses. For all Bayesian analyses, four chains were used with 6000 iterations each. Convergence of the Markov chain Monte Carlo simulations was evaluated via trace plots and model diagnostics provided within the rmsb package [30,32]. Additional details of the statistical analysis plan can be found in the Supplement.

Table 1
Baseline characteristics of the overall cohort.

Characteristic	Lopinavir/ritonavir (N = 220)	Placebo (N = 226)
Age (years), mean (SD)	39.9 (12.2)	41.7 (12.2)
Female sex, n (%)	129 (58.6%)	132 (58.4%)
Race/ethnicity, n (%)[a]		
Non-Hispanic White	170 (77.3%)	184 (81.4%)
Non-Hispanic Black	19 (8.6%)	16 (7.1%)
Non-Hispanic other	8 (3.6%)	10 (4.4%)
Hispanic	20 (9.1%)	13 (5.8%)
Missing	3 (1.4%)	3 (1.3%)
Body mass index (kg/m^2), mean (SD)	29.3 (7.8)	27.9 (6.8)
Number of comorbidities, n (%)[b]		
0	46 (20.9%)	53 (23.5%)
1	86 (39.1%)	85 (37.6%)
≥2	88 (40.0%)	88 (38.9%)
Number of baseline symptoms, n (%)[c]		
1	13 (5.9%)	9 (4.0%)
2	25 (11.4%)	25 (11.1%)
3	48 (21.8%)	42 (18.6%)
4	45 (20.5%)	54 (23.9%)
5	32 (14.5%)	26 (11.5%)
≥6	57 (25.9%)	70 (31.0%)
Symptom duration (days), mean (SD)	4.3 (1.3)	4.2 (1.3)
Vaccination status, n (%)[d]		
Fully vaccinated	45 (20.5%)	48 (21.2%)
Partially vaccinated	17 (7.7%)	21 (9.3%)
Not vaccinated	109 (49.5%)	109 (48.2%)
Unknown	49 (22.3%)	48 (21.2%)

[a] Race/ethnicity as reported by participant.
[b] Comorbidities include class 1-3 obesity, hypertension, coronary artery disease, asthma, chronic obstructive pulmonary disease, diabetes, chronic kidney disease, liver disease, immunosuppressive condition, rheumatologic/autoimmune condition, neurological condition, or blood disorder.
[c] Baseline symptoms include weakness/fatigue, cough, body aches, fever, shortness of breath, diarrhea, chest pain, nausea, and abdominal pain.
[d] Full vs partial vaccination status based on approved number of doses, not vaccinated represents participants enrolled before approved vaccines or reporting not being vaccinated, unknown represents period in trial between vaccine approval and when data was collected on vaccine status.

Role of the funding source

The funding organizations had no direct involvement in the decisions related to the trial, the analysis, or the drafting or revision of the manuscript.

Results

Study enrollment and participant characteristics

From June 2020 to December 2021, investigators at five United States sites enrolled 446 participants from 39 states in the United States (Figure 1). The primary analysis population included 437 patients who received LPV/r (n = 216) or Plb (n = 221). Baseline characteristics were similar between the two treatment groups (Table 1; Appendix Table 1). The mean age was 41 (SD = 12) years, and 78% had at least one comorbid condition associated with risk for severe disease. The average symptom duration before randomization was 4.3 (SD = 1.3) days, with 78% of participants having symptoms for five or fewer days. Over 90% of participants received their randomized treatment the next day after randomization, resulting in an average length of 5.4 (SD = 1.4) days from symptom onset to medication receipt (Appendix Figure 1). The most commonly reported symptoms at baseline were weakness/fatigue (88%), cough (87%), and body aches (79%). The DSMB recommended the trial terminate for futility in December 2021, af-

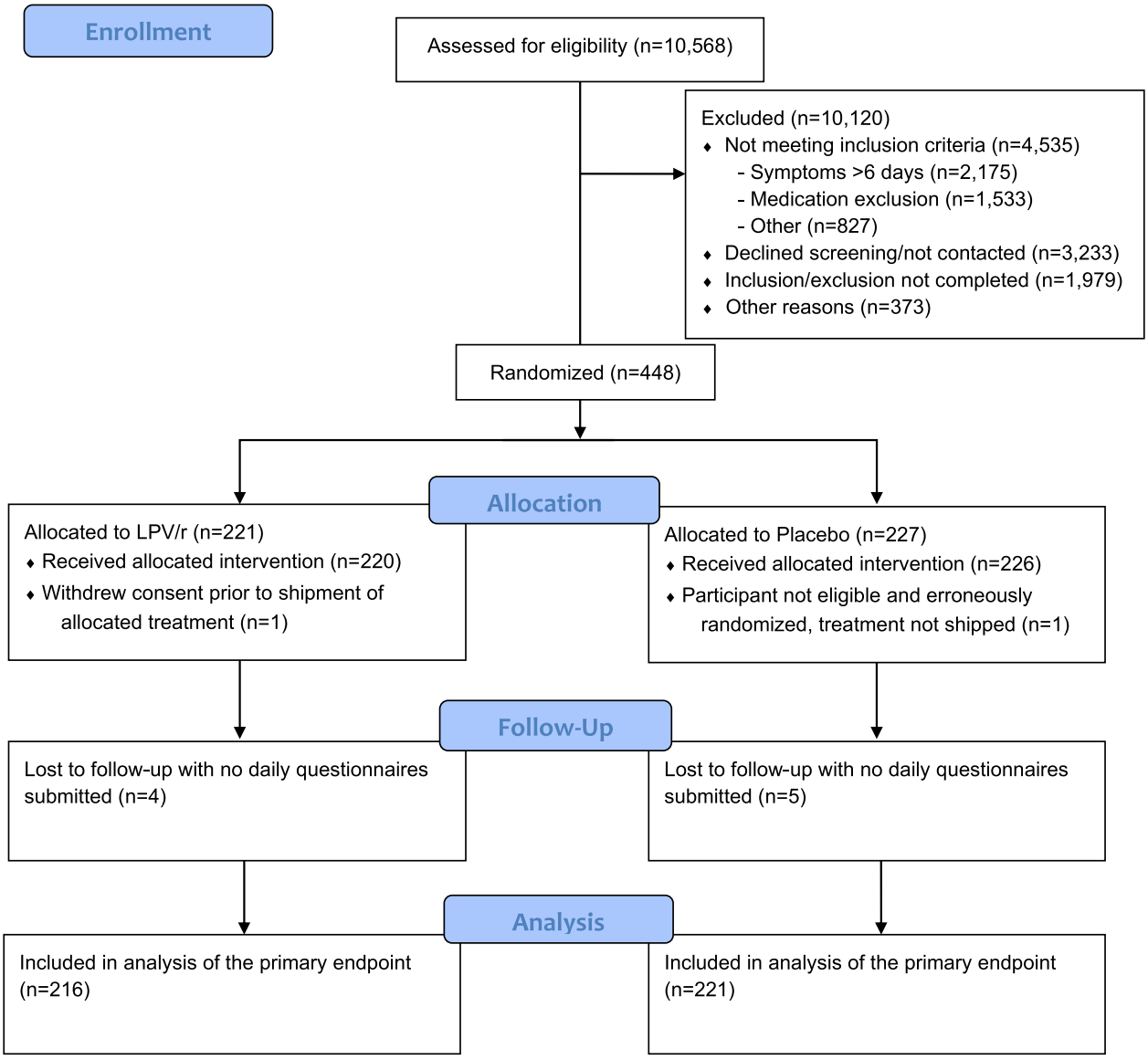

Figure 1. CONSORT diagram.
LPV/r, lopinavir/ritonavir.

ter 415 participants had data for the primary outcome when the probability of observing efficacy at the planned maximum sample size was less than 10%.

Efficacy outcomes

In the primary analysis population, we observed no evidence of a treatment effect over the first 15 study days (Figure 2). The unadjusted odds of LPV/r resulting in a better ordinal category than Plb was 0.97 (95% credible interval [CrI]: 0.67 to 1.40; Pr[OR >1] $=$ 0.44) over the first 15 days after randomization. Similar results were observed after adjusting for other covariates.

Secondary outcomes are presented in Table 2 and Appendix Table 2. There were 3.2% (n $=$ 7) of LPV/r and 2.7% (n $=$ 6) of Plb participants hospitalized within 29 days, with one death reported in the LPV/r arm. The number of fever-free days was similar between groups. Given the limited number of hospitalizations, numbers of oxygen-, intensive care unit-, and hospital-free days were similar between groups, with most participants having all 17 days indicated as free of these outcomes.

Exploratory analyses based on the Bayesian longitudinal proportional odds model for the outcome of the severity of each of the 10 measured symptoms are presented in the online-only Supplement (Appendix Table 3; Appendix Figures 2-11). Compared to Plb, LPV/r had worse odds for more severe diarrhea (OR 0.58, 95% CrI: 0.41, 0.82), with no other symptoms presenting significant differences.

Safety outcomes

Solicited AEs are presented in Table 3. Rates were similar between LPV/r and Plb. Five (2.3%) LPV/r participants reported a severe rash vs no such reports among Plb participants. The one observed death in the LPV/r group due to COVID-19 pneumonia was adjudicated as being unrelated to the study treatment.

Subgroup analyses

Ultimately, no important subgroup differences were detected. Baseline renal function, as measured by chronic kidney disease and dialysis status, was not completed, given only two participants reported chronic kidney disease. Based on the approach to subgroup

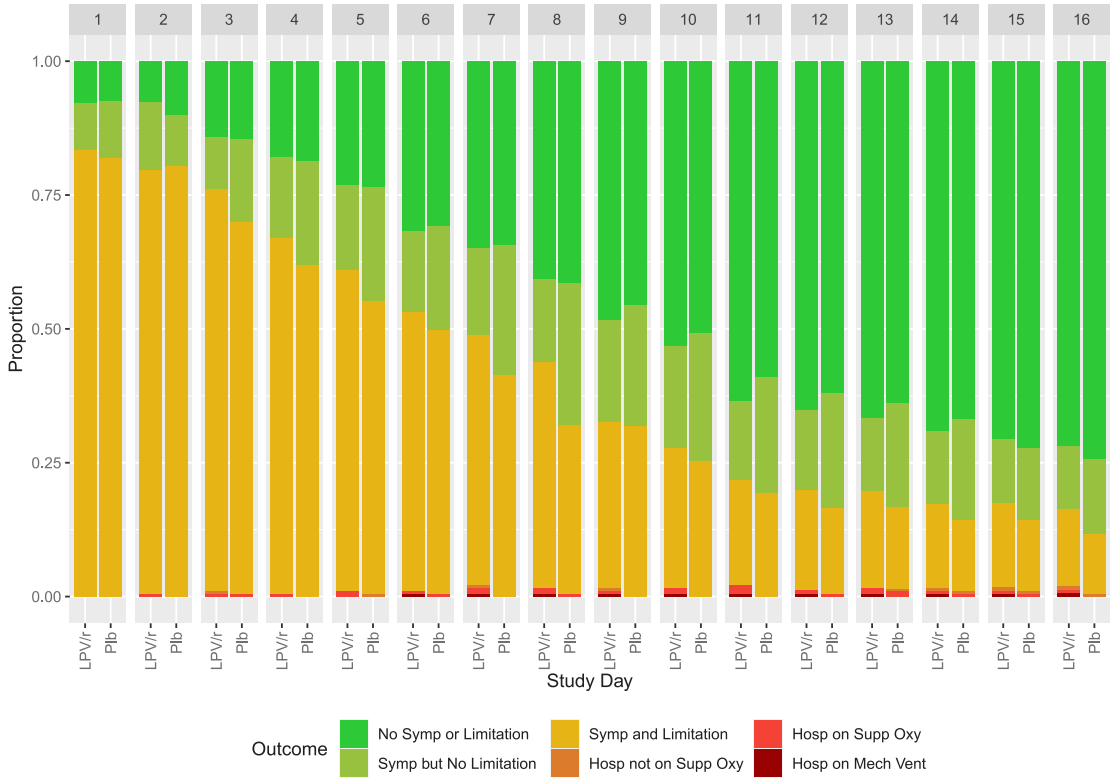

Figure 2. COVID-19 ordinal outcome by study arm and study day.
The unadjusted OR that LPV/r results in a better ordinal category than Plb over the first 15 days after randomization was 0.97 (95% credible interval: 0.67 to 1.40; Pr[OR >1] = 0.44), representing no significant improvement over the course of 15 days.
Hosp, hospitalization; LPV/r, lopinavir/ritonavir; Mech Vent, mechanical ventilation; OR, odds ratio; Plb, placebo; Supp Oxy, supplemental oxygen; Symp, symptoms.

Table 2
Secondary outcomes[a].

Outcome	Lopinavir/ritonavir N = 220	Placebo N = 226
Worst ordinal score over first 15 days		
1: Death	0 (0.0%)	0 (0.0%)
2: Hospitalized on mechanical ventilation/extracorporeal membrane oxygenation	1 (0.5%)	0 (0.0%)
3: Hospitalized on supplemental oxygen	5 (2.3%)	4 (1.8%)
4: Hospitalized not on supplemental oxygen	1 (0.5%)	2 (0.9%)
5: Not hospitalized with symptoms & limitations	187 (86.6%)	191 (86.4%)
6: Not hospitalized with symptoms, no limitations	10 (4.6%)	14 (6.3%)
7: Not hospitalized without symptoms nor limitations	12 (5.6%)	10 (4.5%)
Missing	4	5
All-cause mortality through day 29, n (%)	1 (0.5%)	0 (0.0%)
Hospitalized through day 29, n (%)	7 (3.2%)	6 (2.7%)
Time to hospitalization (days), median (Q1, Q3)	6.0 (4.0, 8.0)	7.0 (5.2, 11.0)
Time to symptom resolution (days), median (Q1, Q3)	11.0 (8.0, 29.0)	11.0 (7.0, 29.0)
Missing	12	5

[a] Appendix Table 1 and the Supplementary Materials present additional secondary outcomes

identification with Bayesian stacking, potential differential treatment effects were identified for race/ethnicity, diabetes mellitus, and duration of symptoms. *Post hoc* analyses also identified potential differences in treatment effects by vaccination status and presence of comorbidities. Appendix Table 4 presents the estimated probability from Bayesian stacking of the model with an interaction between treatment and the subgroup variable being higher than the model without the interaction. The estimated OR and 95% CrIs within subgroups are presented in Appendix Table 5, where all CrIs included OR of one, suggesting no observable benefit of treatment within any subgroup.

Discussion

Early treatment of non-hospitalized patients with LPV/r within 6 days of COVID-19 symptom onset did not improve symptom resolution and hospitalization in non-hospitalized participants with COVID-19 when compared to Plb. There was no evidence that specified subgroups may benefit from the intervention. Secondary and safety outcomes were similar between groups, with a low overall hospitalization rate of 2.9%. Through the novel, decentralized TREAT NOW platform trial, we successfully enrolled patients across the United States using just five enrolling sites, with robust inter-

Table 3
Adverse events.

Symptom	Lopinavir/ritonavir (n = 220)	Placebo (n = 226)
Serious AEs	2 (0.9%)	1 (0.4%)
Protocol-specified AEs		
Seizures	0 (0.0%)	0 (0.0%)
Heart palpitations	12 (5.5%)	15 (6.6%)
Pancreatitis	0 (0.0%)	0 (0.0%)
New kidney problems	0 (0.0%)	1 (0.4%)
Hypoglycemia	3 (1.4%)	2 (0.9%)
Severe skin reaction	5 (2.3%)	0 (0.0%)
Anemia/liver problem/low platelet	3 (1.4%)	3 (1.3%)
Respiratory failure	1 (0.5%)	0 (0.0%)

AE, adverse event.

vention delivery and longitudinal data collection using a remote approach.

There are important elements that make TREAT NOW distinct from other LPV/r COVID-19 clinical trials. First, we focused on non-hospitalized patients rather than those admitted to the hospital for COVID-19 who may be more severely ill and later in the course of illness [26–28]. Second, when comparing to the outpatient TOGETHER trial, which enrolled non-hospitalized patients with COVID-19 and included LPV/r, we enrolled patients earlier in the course of the disease (78% vs 16% enrolled within 5 days of symptom onset) and included a longer treatment duration (14 vs 10 days) [29]. However, despite early interest in this agent, given its putative mechanism as an inhibitor of the 3-CL protease, we found no evidence to support the use of LPV/r for the treatment of COVID-19 in the outpatient setting.

TREAT NOW included other innovations worth noting. The use of daily, longitudinal data collection with Bayesian modeling for the primary outcome analysis facilitated the estimation of missing responses and the ability to use an ordinal scale reflecting a range of participant outcomes over time. Given the desire to reduce contact of study personnel and expand the reach of trial recruiting of non-hospitalized COVID-19 individuals, our study leveraged the ability to remotely enroll and manage participants through the fully decentralized approach. This allowed greater flexibility for participants across the United States since each TREAT NOW site could serve as an enrolling center for non-local participants. Additionally, the use of a central pharmacy with overnight shipping of allocated treatment doses removed the requirement for participants to attend a study site to obtain the investigational drug. Finally, we implemented automated daily surveys to track symptom resolution, safety, and disease progression, which reduced patient-coordinator contact unless necessary for follow-up (i.e., non-response notification, AE trigger). We constructed the surveys to be brief and mobile-friendly to encourage daily participation, which adds validity and power to the outcome assessment. Accordingly, over 83% of potential daily data collection was completed with this approach (Appendix Figure 4). The decentralized nature allowed for targeted advertising via social media to further increase enrollment and representation across a wide range of geographic and socioeconomic groups. The TREAT NOW platform also served as a model for the ongoing ACTIV-6: COVID-19 Study of Repurposed Medications platform trial (NCT04885530).

There are limitations to consider with TREAT NOW. The use of the modified COVID-19 outcomes scale was selected early in the pandemic; as the pandemic continues to evolve, there is growing recognition that the World Health Organization COVID-19 clinical status scale may be suboptimal for outpatient studies. Participants self-reported symptoms via a daily survey, but this could have led to heterogeneity in how severity was considered for each reported symptom. The remote nature of the trial also means that events such as hospitalizations are unlikely to be directly observed and may be undercounted if not reported by participants. While there was some missingness with daily surveys, over 83% of daily surveys were successfully completed, and the use of the Bayesian longitudinal proportional odds regression model facilitated the use of all available information to minimize the influence of missingness on outcomes. Given that the final participants enrolled in December 2021, it is unlikely that many were infected with the Omicron variant. Finally, it may be that the concentrations of LPV/r produced by the dose used in the trial were not high enough to achieve virus neutralization [33–35].

In this innovative, decentralized trial, early administration of LPV/r for non-hospitalized individuals with symptomatic COVID-19 was not shown to improve clinical outcomes, including symptom resolution or disease severity.

Declaration of competing interest

AAG received COVID-19 grant funding during the conduct of the trial from the Department of Defense (DoD), National Institute of Health (NIH), and Centers for Disease Control and Prevention (CDC), and investigator-initiated funding from Faron Pharmaceuticals, outside the current work. TWR serves on a data and safety monitoring board (DSMB) for Sanofi, Inc., and received funding from Cumberland Pharmaceuticals, Inc. and Cytovale, Inc. CJL has grants or contracts from NIH, DoD, CDC, bioMerieux, Entegrion Inc., Endpoint Health, and Astra Zeneca outside the submitted work. No disclosures for AMK, NIS, JW, SMB, BJC, KWH, AEJ, MSP, WHS, CS, SAS, PCN, and BTT.

Funding

This work was supported by the United States Department of Defense (ID07200010-301-2); an investigator-initiated grant from AbbVie, the manufacturer of the study intervention; The National Heart, Lung, and Blood Institute (K01 HL151754 to AMK); and the National Center for Advancing Translational Sciences (UL1TR002243).

Author contributions

Funding was obtained by NIS, TWR, and AAG. The study was designed by AMK, NIS, TWR, CJL, and AAG. The underlying data were verified by AMK, JW, and KWH, and data analyses were done by AMK. AMK wrote the first draft of the manuscript. All authors interpreted data, provided critical review and revision of the text, and approved the final version of the manuscript. AAG takes responsibility for the manuscript as a whole.

Disclaimer

The views expressed are those of the author(s) and do not reflect the official views or policy of the Department of Defense or its Components. The voluntary, fully informed consent of the subjects used in this research was obtained as required by 32 CFR 219 and DODI 3216.02_AFI 40-402.

Data sharing statement

Deidentified data from the Trial of Early Antiviral Therapies during Non-hospitalized Outpatient Window (TREAT NOW) trial will be made available 1 year after publication of final results from the platform by written request, contingent on approval from the trial steering committee. Supporting documents will be made available, including the protocol, statistical analysis plan, informed consent document, and data dictionary. Data will be made available to researchers after approval of a proposal for use of the data.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.12.028.

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